American Journal of Epidemiology

Vol. 162, No. 12
DOI: 10.1093/aje/kwi341
Advance Access publication October 26, 2005

Original Contribution

Immune-Related Conditions and Immune-Modulating Medications as Risk Factors for Non-Hodgkin's Lymphoma: A Case-Control Study

Eric A. Engels[1], James R. Cerhan[2], Martha S. Linet[1], Wendy Cozen[3], Joanne S. Colt[1], Scott Davis[4], Gloria Gridley[1], Richard K. Severson[5], and Patricia Hartge[1]

[1] Division of Cancer Epidemiology and Genetics, National Cancer Institute, Department of Health and Human Services, Rockville, MD.
[2] Department of Health Sciences Research, Mayo Clinic College of Medicine, Rochester, MN.
[3] Department of Preventative Medicine, Norris Comprehensive Cancer Center, University of Southern California School of Medicine, Los Angeles, CA.
[4] Program in Epidemiology, Fred Hutchinson Cancer Research Center, Seattle, WA.
[5] Department of Family Medicine and Karmanos Cancer Institute, Wayne State University, Detroit, MI.

Received for publication March 4, 2005; accepted for publication July 18, 2005.

In immunosuppressed or autoimmune disease states, disordered immune responses may lead to non-Hodgkin's lymphoma (NHL). In a US population-based case-control study of NHL (1998–2000), the authors collected personal histories of immune-related conditions and use of immune-modulating therapies as well as family histories of autoimmune conditions. The study included 1,321 NHL cases and 1,057 controls; only half received some questionnaire components. NHL was associated with Sjögren's syndrome (odds ratio (OR) = 13, 95% confidence interval (CI): 1.7, 100) and lupus (OR = 4.2, 95% CI: 1.2, 15). Two specific NHL subtypes were strongly associated with Sjögren's syndrome: salivary gland (OR = 290, 95% CI: 33, 2600) and marginal zone (OR = 75, 95% CI: 9.1, 610). NHL was less convincingly associated with receipt of an organ transplant (OR = 2.0, 95% CI: 0.4, 11). Other autoimmune conditions were too rare to evaluate or not associated with NHL. Corticosteroid use was unrelated to NHL (OR = 1.0, 95% CI: 0.8, 1.2), but methotrexate use was marginally associated (OR = 2.3, 95% CI: 0.7, 7.5). Family history of dermatomyositis was associated with NHL (7 cases vs. 0 controls, OR = infinite; two-sided p = 0.02), but dermatomyositis was absent in cases themselves. Family history of remaining conditions was unrelated to NHL. Results suggest that disordered immunity in some immune-related conditions can lead to NHL.

autoimmune diseases; case-control studies; immunosuppression; lymphoma, non-Hodgkin; methotrexate; organ transplantation; risk factors; Sjogren's syndrome

Abbreviations: CI, confidence interval; NHL, non-Hodgkin's lymphoma; OR, odds ratio; SEER, Surveillance, Epidemiology, and End Results; SLE, systemic lupus erythematosus.

The etiology of non-Hodgkin's lymphoma (NHL) is largely unknown. Under normal conditions, T and B lymphocytes respond to antigenic challenges in a regulated manner, and proliferative responses are self-limited. However, in immunosuppressed disease states (e.g., following receipt of an organ transplant or in acquired immunodeficiency syndrome), disordered immune responses characterized by continued lymphocyte proliferation can eventually lead to NHL (1). Epstein-Barr virus may be an important contributor in the high-grade NHLs that develop in immunocompromised

Correspondence to Dr. Eric A. Engels, Viral Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, DHHS, 6120 Executive Boulevard, EPS 8010, Rockville, MD 20852 (e-mail: engelse@exchange.nih.gov).

individuals (2). Nonetheless, most NHLs arise in the absence of obvious immunosuppressive disorders.

Autoimmune conditions have attracted substantial attention as possible predisposing conditions for NHL. These idiopathic diseases are characterized by disregulated lymphocyte reactivity against self-antigens and the production of autoantibodies, leading to damage of the targeted tissues (e.g., joints, skin) (3). By analogy with what is observed in immunosuppressed states, the ongoing abnormal lymphocyte activation present in autoimmune disorders could predispose to NHL. Indeed, cohort studies of individuals with systemic lupus erythematosus (SLE), rheumatoid arthritis, and rarer conditions such as Sjögren's syndrome have provided evidence that these individuals have an increased risk of NHL (4–11). Still, cohort studies have usually followed up only those individuals with a single autoimmune condition, often with especially severe manifestations. In addition, cohort studies have generally observed few NHL outcomes, which have not always been well characterized. A case-control study of NHL offers a complementary approach. Several case-control studies of NHL have examined the associations with the more common autoimmune conditions (e.g., rheumatoid arthritis) or all autoimmune conditions taken together, but they have not provided detailed data that would allow a systematic evaluation of NHL risk in relation to the full spectrum of autoimmune conditions (12–15).

In the present analysis, we used data from a large, population-based US case-control study of NHL to examine the associations of various immune-related conditions (i.e., autoimmune conditions and receipt of an organ transplant) with NHL. We also studied whether NHL risk was elevated for individuals who received selected immune-modulating medications or had a family history of autoimmune conditions. Finally, we sought to characterize whether these factors were related to particular NHL subtypes defined by histology or anatomic site.

MATERIALS AND METHODS

Study design and questionnaire data

The National Cancer Institute-Surveillance, Epidemiology, and End Results (SEER) case-control study has been described previously (16, 17). Briefly, between July 1998 and June 2000, subjects uninfected with human immunodeficiency virus were enrolled in four US SEER registry areas: Iowa State and metropolitan Detroit, Michigan; Los Angeles, California; and Seattle, Washington. The study was approved by institutional review boards at the National Cancer Institute and participating registries, and participants provided written informed consent.

Eligible cases were individuals with incident NHL (aged 20–74 years) identified by the SEER registries (18). Of 2,248 potentially eligible cases, 320 (14 percent) died before we could conduct an interview, 127 (6 percent) could not be located, 16 (1 percent) had moved out of the area, and, for 57 (3 percent), the physician refused participation. We attempted to contact the remaining 1,728; 1,321 (76 percent) participated. Controls were selected from the general population in the four areas, stratified by age, sex, and race, and were identified by using random digit dialing (aged 20–64 years) or Medicare eligibility files (aged 65–74 years). Of 2,409 potential controls selected, 28 (1 percent) died before we could contact them, 311 (13 percent) could not be located, and 24 (1 percent) had moved out of the area. We attempted to contact the remaining 2,046 subjects; 1,057 (52 percent) participated. Response rates were higher for some demographic subgroups, including women (17).

Study subjects completed a computer-assisted personal interview in their home and provided a blood or buccal cell sample (16). In the interview, the 1-year period prior to interview was excluded from medical history questions to avoid confusion with symptoms possibly related to incipient NHL. All subjects were asked about a history of specific medical conditions, including immune-related disorders (''Were you ever told by a doctor or other health professional that you had CONDITION?''), and use of corticosteroids (''Before one year ago, did you ever take corticosteroids, such as cortisone or prednisone?''). Subjects who answered in the affirmative were then asked to specify the age at diagnosis or (for corticosteroids) age at first use. Because of the length and complexity of the overall interview, by design some questionnaire components were administered to only half of the subjects. ''Questionnaire A,'' which included an especially detailed medical history and a family history, was given to all African-American subjects and, by random selection, to half of the other subjects. Family history questions inquired whether first-degree relatives (specified separately as father, mother, siblings, children) had any of the autoimmune conditions of interest. Questionnaire A also contained questions regarding use of methotrexate and gold injections. Remaining subjects answered ''questionnaire B,'' which did not include information on family history.

All NHLs were confirmed histologically. Information on NHL histology and anatomic site was obtained from reports supplied to the SEER registries. Histologic diagnoses were coded by using the *International Classification of Diseases for Oncology*, Second Edition (19) and were subsequently translated to categories of the World Health Organization classification (20).

Statistical methods

We calculated odds ratios to assess the association between various immune-related medical conditions and NHL. Similarly, we measured associations between NHL and variables describing medication use and family history (summarized as any vs. no first-degree relative with the condition). Odds ratios were adjusted with logistic regression for the variables used in control sampling (age, sex, race, study site), unless there were too few subjects with the condition of interest for the model to converge, in which instance we calculated an unadjusted odds ratio. We did not calculate any odds ratio when the number of subjects with the condition was five or fewer. In this paper, we present 95 percent confidence intervals using the Wald method. We also present p values derived by using a score test, which is more accurate than the Wald statistic for sparse data,

TABLE 1. Characteristics of NHL* cases and controls from the NCI-SEER* study, United States, 1998–2000

Characteristic	All subjects				Subjects who responded to a detailed medical history questionnaire			
	Cases ($n = 1,321$)		Controls ($n = 1,057$)		Cases ($n = 759$)		Controls ($n = 589$)	
	No.	%	No.	%	No.	%	No.	%
Sex								
Male	711	53.8	546	51.7	410	54.0	304	51.6
Female	610	46.2	511	48.3	349	46.0	285	48.4
Age at diagnosis or selection (years)								
20–34	81	6.1	58	5.5	43	5.7	41	7.0
35–44	166	12.6	104	9.8	89	11.7	64	10.9
45–54	289	21.9	196	18.5	168	22.1	125	21.2
55–64	350	26.5	253	23.9	206	27.1	135	22.9
65–74	435	32.9	446	42.2	253	33.3	224	38.0
Race								
White	1,123	85.0	843	79.8	604	79.6	407	69.1
African American†	110	8.3	151	14.3	100	13.2	145	24.6
Other	88	6.7	63	6.0	55	7.3	37	6.3
Study site								
Detroit, Michigan	319	24.2	214	20.3	238	31.4	138	23.4
Iowa	361	27.3	276	26.1	170	22.4	124	21.1
Los Angeles, California	319	24.2	273	25.8	187	24.6	172	29.2
Seattle, Washington	322	24.4	294	27.8	164	21.6	155	26.3
Education (no. of years)‡								
0–11	128	9.7	111	10.5	85	11.2	61	10.4
12–15	815	61.7	616	58.3	471	62.1	361	61.3
≥16	377	28.6	330	31.2	202	26.7	167	28.4

* NHL, non-Hodgkin's lymphoma; NCI-SEER, National Cancer Institute-Surveillance, Epidemiology, and End Results.

† Sixteen African-American subjects were inadvertently not administered the questionnaire with detailed medical history (questionnaire A).

‡ Data on education were missing for one case.

although we note that the Wald p value was generally close to the score test p value. For comparisons in which no odds ratio could be calculated (zero cases or controls with the condition), we report the Fisher's exact test p value. All p values are two sided.

For the minority of subjects who were administered a given questionnaire but did not respond to a specific question or did not know the answer, we considered them as not having the condition of interest (analyses in which these subjects were excluded produced similar results). We also conducted more detailed analyses for some conditions, as suggested by an overall positive association with NHL in the present study or prior reports. We characterized the duration of the immune-related condition or use of medication among cases and, when possible, examined the relation between duration and NHL risk. In this paper, we also describe the distribution of NHL subtypes by histology and site among cases with specific conditions of interest, medication history, or family history.

RESULTS

Description of NHL cases and controls

Cases ($n = 1,321$) and controls ($n = 1,057$) were demographically similar, although controls were slightly older and more likely to be African American (table 1). Slightly more than half of the subjects (759 cases, 589 controls) were administered questionnaire A, which included an extended medical and family history. This subgroup generally resembled the larger group of all subjects, although, by design, it included a greater proportion of African Americans (table 1).

The 1,321 NHLs were classified histologically as diffuse large B cell ($n = 417$, 31.6 percent), follicular ($n = 319$, 24.1 percent), small lymphocytic ($n = 161$, 12.2 percent), marginal zone ($n = 106$, 8.0 percent), mantle zone ($n = 50$, 3.8 percent), Burkitt's ($n = 20$, 1.5 percent), T cell ($n = 82$, 6.2 percent), or other/unspecified ($n = 166$, 12.6 percent) subtype. Most NHLs ($n = 852$, 64.5 percent) arose in lymph

TABLE 2. Associations between NHL* case-control status and immune-related medical conditions in the NCI-SEER* study, United States, 1998–2000†

Medical condition	Cases		Controls		Adjusted OR*,‡	95% CI*	*p* value§
	No.	%	No.	%			
Conditions for which all subjects provided data (n = 1,321 cases; n = 1,057 controls)							
Receipt of an organ transplant	5	0.4	2	0.2	2.0	0.4, 11	0.42
Sjögren's syndrome	15	1.1	1	0.1	13	1.7, 100	0.001
Primary	5	0.4	1	0.1	4.9	0.6, 43	0.11
Secondary	10	0.8	0	0	∞		0.003
Lupus	14	1.1	3	0.3	4.2	1.2, 15	0.02
Systemic lupus erythematosus	5	0.4	3	0.3	1.3	0.3, 5.6	0.72
Other/unknown type	9	0.7	0	0	∞		0.006
Inflammatory bowel disease¶	29	2.2	19	1.8	1.2	0.7, 2.1	0.58
Crohn's disease	10	0.8	5	0.5	1.5	0.5, 4.3	0.50
Ulcerative colitis	22	1.7	16	1.5	1.1	0.6, 2.1	0.80
Rheumatic heart disease	25	1.9	19	1.8	1.1	0.6, 2.1	0.73
Polymyalgia rheumatica	4	0.3	6	0.6	0.7	0.2, 2.5	0.56
Sarcoidosis	5	0.4	5	0.5	0.7	0.2, 2.6	0.61
Multiple sclerosis	2	0.2	4	0.4	0.4	0.1, 2.2	0.27
Uveitis	1	0.1	3	0.3			
Myasthenia gravis	1	0.1	1	0.1			
Polymyositis	0	0	1	0.1			
Dermatomyositis	0	0	0	0			
Celiac disease	0	0	0	0			
Conditions for which only those subjects responding to the detailed medical history questionnaire provided data (n = 759 cases; n = 589 controls)							
Arthritis#	206	27.1	164	27.8	1.0	0.8, 1.4	0.74
Rheumatoid arthritis	48	6.3	34	5.8	1.3	0.8, 2.1	0.24
Osteoarthritis	91	12.0	83	14.1	0.8	0.6, 1.2	0.31
Other/unspecified arthritis	84	11.1	57	9.7	1.2	0.9, 1.8	0.26
Juvenile-onset diabetes mellitus	1	0.1	1	0.2			

* NHL, non-Hodgkin's lymphoma; NCI-SEER, National Cancer Institute-Surveillance, Epidemiology, and End Results; OR, odds ratio; CI, confidence interval.

† Results are shown separately for immune-related medical conditions for which all subjects provided data and for conditions for which data were provided by only those subjects responding to a detailed medical history questionnaire (questionnaire A; refer to the Materials and Methods section of the text). In each group, the conditions are ordered according to the magnitude of association with NHL or, if this was not calculated, by the prevalence of the condition among study subjects. The exception is receipt of an organ transplant, which is listed first in the table.

‡ Adjusted for age, sex, race, and study site. Odds ratios were not calculated if five or fewer subjects reported the condition.

§ Calculated by using a score test, except for secondary Sjögren's syndrome and lupus of other/unknown type, for which Fisher's exact test was used. All *p* values are two sided.

¶ Five subjects reported both Crohn's disease and ulcerative colitis.

Subjects who stated that they had arthritis but for whom information on type of arthritis was not provided were treated as having "unspecified" arthritis. Some subjects reported more than one type of arthritis.

nodes, while the remainder were extranodal ($n = 430$, 32.6 percent) or involved an unspecified site ($n = 39$, 3.0 percent).

Associations of NHL with immune-related medical conditions

Receipt of an organ transplant was associated with a twofold increased risk of NHL, although this increase was not significant (table 2). Transplanted organs included the kidney ($n = 3$), kidney and pancreas ($n = 1$), liver ($n = 2$), and heart ($n = 1$). NHL developed a median of 10 years after transplantation (range, 1–22 years). Four NHLs in transplant recipients were diffuse large B cell, and one was a Burkitt's. By site, four NHLs were nodal and one arose in the small intestine.

We observed a strongly increased risk of NHL associated with Sjögren's syndrome (adjusted odds ratio (OR) = 13,

TABLE 3. Associations between NHL* case-control status and use of immune-modulating medications in the NCI-SEER* study, United States, 1998–2000

Medication	Cases		Controls		Adjusted OR*,†	95% CI*	*p* value‡
	No.	%	No.	%			
*Medications for which all subjects provided data (*n = *1,321 cases;* n = *1,057 controls)*							
Corticosteroids							
Any use	376	28.5	304	28.8	1.0	0.8, 1.2	1.00
Total duration of use (no. of days)							
1–19	211	16.0	176	16.7	1.0	0.8, 1.2	
20–99	59	4.5	52	4.9	0.9	0.6, 1.3	
≥100	35	2.7	31	2.9	0.9	0.6, 1.5	
Unknown	71	5.4	45	4.3	1.2	0.8, 1.8	
*Medications for which only those subjects responding to a detailed medical history questionnaire provided data (*n = *759 cases;* n = *589 controls)*							
Methotrexate, any use	10	1.3	4	0.7	2.3	0.7, 7.5	0.17
Gold, any use§	6	0.8	3	0.5	1.6	0.4, 6.2	0.53

* NHL, non-Hodgkin's lymphoma; NCI-SEER, National Cancer Institute-Surveillance, Epidemiology, and End Results; OR, odds ratio; CI, confidence interval.

† Adjusted for age, sex, race, and study site, unless stated otherwise.

‡ Calculated by using a score test. All *p* values are two sided.

§ Data on gold use were obtained only from those individuals who stated that they had arthritis; thus, subjects who stated that they did not have arthritis were assumed not to have received gold injections. The odds ratio presented is unadjusted, because the adjusted regression model did not converge.

table 2). All individuals with Sjögren's syndrome were female, but the association with NHL was unchanged when analysis was restricted to females (adjusted OR = 14, 95 percent confidence interval (CI): 1.9, 110; $p < 0.001$). Six individuals with Sjögren's syndrome reported no other autoimmune condition (i.e., primary Sjögren's syndrome), while 10 also reported other autoimmune diseases (seven rheumatoid arthritis, two lupus, one sarcoidosis: secondary Sjögren's syndrome). Associations with NHL were apparent for both primary and secondary Sjögren's syndrome (table 2). Among the 15 cases with Sjögren's syndrome, five (33.3 percent) had a salivary gland NHL (parotid gland in each instance). In comparison, only 18 (1.4 percent) of the remaining 1,306 NHL cases had a salivary gland NHL. Close to half of the NHLs in individuals with Sjögren's syndrome were classified as marginal zone ($n = 7$). The remainder included small numbers of follicular ($n = 2$), diffuse large B cell ($n = 2$), lymphoplasmacytic ($n = 1$), T cell ($n = 1$), or unspecified ($n = 2$) subtype. All five salivary gland NHLs in individuals with Sjögren's syndrome were marginal zone. Sjögren's syndrome was thus associated with greatly increased risk of salivary gland NHL (unadjusted OR = 290, 95 percent CI: 33, 2,600; $p < 0.001$), marginal zone NHL (unadjusted OR = 75, 95 percent CI: 9.1, 610; $p < 0.001$), and, specifically, marginal zone NHL of the salivary gland (unadjusted OR = 880, 95 percent CI: 89, 8,700; $p < 0.001$). Among 11 NHL cases with Sjögren's syndrome who supplied information, the median duration of Sjögren's syndrome was 7 years (range, 2–19).

Individuals with lupus experienced a fourfold increased risk of NHL (table 2). Approximately half of lupus patients specifically described SLE ($n = 8$), while the remainder largely reported poorly specified subtypes: discoid ($n = 2$), drug induced ($n = 1$), early/incompletely diagnosed ($n = 2$), or unspecified ($n = 4$). NHL was not significantly associated with SLE but was strongly associated with other/unknown lupus subtypes (table 2). The most common histologic subtype of NHL was follicular ($n = 5$), followed by marginal zone ($n = 3$), diffuse large B cell ($n = 2$), and other/unspecified ($n = 4$) subtypes. Among cases with lupus, 10 NHLs were nodal and four were extranodal or of unknown site. Two cases had both lupus and Sjögren's syndrome. The median duration of lupus was 19 years (range, 3–48 years) among eight NHL cases who provided data.

NHL was not significantly associated with a history of rheumatoid arthritis (OR = 1.3, table 2) or with duration of rheumatoid arthritis (not shown; median duration, 12 years; range, 1–51 years among cases). For cases with rheumatoid arthritis, NHLs were classified histologically as diffuse large B cell ($n = 14$), marginal zone ($n = 10$), follicular ($n = 8$), small lymphocytic ($n = 6$), lymphoplasmacytic ($n = 2$), T cell ($n = 4$), or other/unspecified ($n = 4$) subtype. Twenty-five NHLs were nodal and 23 were extranodal. Seven cases with rheumatoid arthritis also had Sjögren's syndrome. Four cases with rheumatoid arthritis had salivary gland NHL, but only one of them also had Sjögren's syndrome.

Associations of NHL with immune-modulating medications

Among both cases and controls, prior use of corticosteroids was common, but use of these medications was unrelated to NHL risk, both overall and when duration of use was considered (table 3). Reasons for corticosteroid use

TABLE 4. Associations between NHL* case-control status and family history of autoimmune medical conditions in the NCI-SEER* study, United States, 1998–2000†

Family history	Cases ($n = 759$)		Controls ($n = 589$)		Adjusted OR*,‡	95% CI*	p value§
	No.	%	No.	%			
Sjögren's syndrome	0	0	3	0.5			
Lupus	16	2.1	20	3.4	0.7	0.3, 1.4	0.27
Inflammatory bowel disease	37	4.9	29	4.9	0.9	0.5, 1.4	0.59
Crohn's disease	9	1.2	4	0.7	1.4	0.4, 4.8	0.55
Ulcerative colitis	29	3.8	25	4.2	0.8	0.5, 1.4	0.43
Rheumatic heart disease	63	8.3	36	6.1	1.3	0.9, 2.1	0.18
Polymyalgia rheumatica	8	1.1	3	0.5	1.6	0.4, 6.1	0.51
Sarcoidosis	4	0.5	6	1.0	0.7	0.2, 2.6	0.58
Multiple sclerosis	10	1.3	6	1.0	1.5	0.5, 4.4	0.44
Uveitis	2	0.3	0	0			
Myasthenia gravis	4	0.5	1	0.2			
Polymyositis	3	0.4	2	0.3			
Dermatomyositis	7	0.9	0	0	∞		0.02
Celiac disease	6	0.8	1	0.2	4.7	0.5, 40	0.12
Rheumatoid arthritis	130	17.1	111	18.9	0.9	0.7, 1.2	0.34
Juvenile-onset diabetes mellitus	13	1.7	8	1.4	1.2	0.5, 3.0	0.69

* NHL, non-Hodgkin's lymphoma; NCI-SEER, National Cancer Institute-Surveillance, Epidemiology, and End Results; OR, odds ratio; CI, confidence interval.

† Medical conditions are ordered as in table 2. Only some subjects were administered a questionnaire that included items regarding family history (questionnaire A) and provided data for these analyses (refer to the Materials and Methods section of the text).

‡ Adjusted for age, sex, race, and study site. Odds ratios were not calculated if five or fewer subjects reported the condition.

§ Derived by using a score test, except for family history of dermatomyositis, where the Fisher's exact test was used. All p values are two sided.

were specified for only 21 percent of the subjects and varied widely (not shown). Among subjects who had Sjögren's syndrome, lupus, or rheumatoid arthritis, corticosteroid use was reported by 63 percent, 76 percent, and 52 percent, respectively (although reasons for use were mostly unspecified). For subjects with these autoimmune conditions, there was a nonsignificantly increased risk of NHL with corticosteroid use (unadjusted OR = 1.7, 95 percent CI: 0.7, 3.7; $p = 0.22$). Among subjects not known to have these conditions, corticosteroid use was not associated with NHL risk (unadjusted OR = 0.9, 95 percent CI: 0.8, 1.1; $p = 0.48$).

Prior use of methotrexate was infrequent but was marginally associated with a doubling of NHL risk (table 3). Ten (71 percent) subjects who had used methotrexate had rheumatoid arthritis, of whom three also had Sjögren's syndrome. Among cases who had used methotrexate, NHLs were classified as marginal zone ($n = 4$), diffuse large B cell ($n = 2$), and other/unspecified ($n = 4$) subtypes. NHLs in methotrexate users were nodal ($n = 5$) or arose at various extranodal sites, including salivary gland ($n = 2$), conjunctiva ($n = 1$), buccal mucosa ($n = 1$), and lung ($n = 1$). All six cases for whom data were available on duration of use had used methotrexate for fewer than 100 days. Gold injections were reported by nine subjects with arthritis (seven of whom had rheumatoid arthritis) but were not significantly associated with NHL (table 3).

Associations of NHL with family history of autoimmune conditions

Table 4 shows associations between NHL and subjects' family history of specific autoimmune conditions. NHL was significantly related to family history of dermatomyositis (seven cases vs. 0 controls, $p = 0.02$). NHLs associated with a family history of dermatomyositis were of the follicular ($n = 3$), diffuse large B cell ($n = 3$), or marginal zone ($n = 1$) subtype. Four were nodal and three were extranodal. In addition, NHL was marginally associated with family history of celiac disease (table 4). One such NHL arose in the ileum (diffuse large B cell subtype), while the others were nodal.

DISCUSSION

In the present case-control study, we systematically examined the associations with NHL across immune-related conditions and characterized NHL subtypes related to each

condition. The strongest association that we observed with NHL was for Sjögren's syndrome (OR = 13). We also found evidence for a smaller increase in NHL risk associated with lupus, and a weaker, nonsignificant association with receipt of an organ transplant.

Sjögren's syndrome is an autoimmune condition of unknown etiology that affects mostly women. It is characterized clinically by the variable presence of parotid gland enlargement, xerostomia, and keratoconjunctivitis sicca and pathologically by the infiltration of lymphocytes into salivary and lacrimal glands (21). Kassan et al. (11) first described a markedly excess risk of lymphoma in Sjögren's syndrome (standardized incidence ratio = 44 compared with the general population). Lymphoma risk in Sjögren's syndrome increases with the severity of inflammation, as indicated by parotid gland enlargement, decreased complement levels, or cutaneous vasculitis (11, 22). We observed extraordinarily elevated risks of salivary gland NHL, marginal zone NHL, and, specifically, marginal zone NHL of the salivary gland for Sjögren's syndrome patients (OR = 290, OR = 75, and OR = 880, respectively). Others have previously noted a relation between Sjögren's syndrome and marginal zone NHL of the salivary gland (23–25). The high risk of these lymphomas suggests that they originate locally as a consequence of chronic lymphocyte activation related to the autoimmune disease process itself. This mechanism could be especially likely for marginal zone NHLs, for which the site of involvement frequently reflects a preceding localized immune response (26).

Somewhat unexpectedly, we found only a nonsignificant, twofold elevation in NHL risk for organ transplant recipients, substantially lower than observed in cohort studies of transplant recipients, which have reported standardized incident ratios for NHL of 6–40 (27–30). The difference between our finding and previous results may be due to several factors. First, NHL represents only one end of a spectrum of posttransplant lymphoproliferative disorder, which also includes more benign reactive hyperplasia and polymorphic lymphoproliferations (20). Because classification of posttransplant lymphoproliferative disorder has changed over time, and because SEER captures only those cases considered to be NHL, we might have included fewer cases than previous studies did. Second, although the overall risk of posttransplant lymphoproliferative disorder has remained constant during the last 15 years (31), changes in organ transplantation practices or immunosuppression regimens could have affected the spectrum of posttransplant lymphoproliferative disorder. Third, our estimate of the association with NHL was imprecise, and the upper limit of our confidence interval for the odds ratio is consistent with prior standardized incidence ratio estimates.

Previous cohort studies have found that individuals with lupus and rheumatoid arthritis are at increased risk of NHL (standardized incidence ratios = 3–5 for lupus and 2–3 for rheumatoid arthritis) (4–10, 32, 33). We found a similar association between lupus and NHL (OR = 4.2), but this association appeared limited to the heterogeneous group of individuals with lupus subtypes other than SLE. Nonetheless, given the small number of individuals with a history of SLE and lack of documentation regarding lupus diagnoses, we cannot rule out an association between SLE and NHL. Some cohort studies of individuals with rheumatoid arthritis (7, 9, 10), though not all (8, 33), have included only hospitalized patients, who presumably had especially severe arthritis. By contrast, our study evaluated NHL risk related to any history of rheumatoid arthritis. Our modest odds ratio estimate for rheumatoid arthritis is in accord with estimates from prior case-control studies (13–15), suggesting that NHL risk might be increased for only those individuals with especially severe rheumatoid arthritis (34).

Although the excess risk of NHL seen for individuals with autoimmune conditions might be due to the immune disregulation characteristic of the condition itself, at least two other explanations have been proposed. First, increased NHL risk may be partly due to treatment with immune-modulating medications (35). Kamel et al. (36) described the occurrence of Epstein-Barr-virus-positive lymphomas in patients receiving methotrexate for rheumatoid arthritis or dermatomyositis, which resolved upon discontinuation of the methotrexate. Of interest, in addition to having immunosuppressing effects, methotrexate can act directly to activate Epstein-Barr virus replication (37). In our study, even though duration of use was generally brief, methotrexate was marginally associated with increased NHL risk. Existing data regarding corticosteroid use have been inconclusive, with several studies finding modestly increased NHL risk related to corticosteroid use (ORs or standardized incidence ratios = 1.2–1.7) (15, 38–40). We did not find strong evidence for an association with corticosteroid use, but we did not have information on specific corticosteroid medications, doses, or routes of administration. Unfortunately, we could not completely separate the effects of these medications from those of the autoimmune conditions. Indeed, we found evidence for increased NHL risk associated with corticosteroids when we restricted analysis to those individuals with Sjögren's syndrome, lupus, or rheumatoid arthritis, suggesting that use of corticosteroid might have been a marker for severity of the underlying autoimmune disease. Likewise, the majority of methotrexate users were individuals with these same autoimmune conditions. Finally, there is substantial interest in whether new agents for the treatment of rheumatoid arthritis, which block tumor necrosis factor, increase NHL risk (32, 41). Because these medications have been introduced only recently, we could not examine their potential association with NHL.

Second, the associations might be explained by an underlying genetic predisposition to both the autoimmune condition and NHL. If so, NHL should be associated with a family history of the autoimmune condition. Our data, although somewhat limited by small numbers, do not support this hypothesis. A family history of dermatomyositis was present solely among cases, but the NHL subtypes in these individuals varied substantially, and no case *himself* had dermatomyositis. Similarly, although we observed a nonsignificant association between NHL and family history of celiac disease, no NHL case had celiac disease. Our null finding regarding a family history of rheumatoid arthritis confirms the results of a prior registry-based linkage study in Sweden (9).

Several study limitations should be acknowledged. First, most immune-related conditions are uncommon. Thus,

although our study was relatively large, it lacked statistical power to identify associations for the least common autoimmune conditions, and our estimates of risk related to these conditions, especially for specific NHL subtypes, were unstable. We were similarly limited in our ability to explore associations with methotrexate use or specific family histories. A related problem due to the sparseness of the data was that regression models adjusting for the study matching factors did not converge for a few conditions; while we present unadjusted odds ratios and tests of significance in these instances, these results could have been biased by the original matching (42). Second, the participation rates were somewhat low, although they were similar to those reported in other recent population-based case-control studies with in-home interviews. The impact of these low rates on our results is difficult to evaluate. It is unlikely, for instance, that the strong association between Sjögren's syndrome and specific NHL subtypes was due solely to a bias introduced by nonparticipation. Indeed, participation rates must differ systematically and substantially between cases and controls for observed associations to be appreciably affected. Third, medical conditions and medication use were self-reported. Because we did not review medical records, we could have misclassified autoimmune conditions, which can resemble one another clinically. This misclassification may have been true especially for rheumatoid arthritis, since the prevalence among our controls (5.8 percent) was somewhat higher than the 0.9 percent prevalence estimated for the general US population based on published studies (43). We suspect that this difference partly reflects inaccurate reporting of rheumatoid arthritis diagnoses by our subjects and partly that previous prevalence estimates may have missed mild arthritis cases. If some of our study subjects reporting rheumatoid arthritis actually had other conditions (e.g., osteoarthritis), our odds ratio estimate could have been biased.

On the other hand, our study had several strengths. Its population-based case-control design enabled us to study a representative sample of NHL cases and the general population. We also had detailed data on the histologic subtypes and anatomic sites of these NHLs.

In conclusion, our results indicate that several immune-related conditions are associated with an increased risk of NHL. Further investigations into the relation between autoimmune conditions and NHL appear warranted. Additional information regarding associations of NHL with rarer autoimmune conditions may derive from pooling data from multiple case-control studies.

ACKNOWLEDGMENTS

Support for this study included contracts N01-PC-67010, N01-PC-67008, N02-PC-71105, N01-PC-67009, and N01-PC-65064 with the National Cancer Institute (Rockville, Maryland).

The authors gratefully acknowledge the contributions of the SEER centers of Detroit, Iowa, Los Angeles, and Seattle for rapid identification of cases; the Centers for Medicare and Medicaid Services for selection of older controls; Carol Haines (Westat, Rockville, Maryland) for development of study materials and procedures, selection of younger controls, and study coordination; Peter Hui and Michael Stagner (Information Management Services, Silver Spring, Maryland) for computer programming support; and Geoffrey Tobias (National Cancer Institute) for research assistance.

Conflict of interest: none declared.

REFERENCES

1. Scherr PA, Mueller NE. Non-Hodgkin's lymphomas. In: Schottenfeld D, Fraumeni JF Jr, eds. Cancer epidemiology and prevention. 2nd ed. New York, NY: Oxford University Press, 1996:920–45.
2. Epstein-Barr virus and Kaposi's sarcoma herpesvirus/human herpesvirus 8. IARC monographs on the evaluation of carcinogenic risks to humans. Vol 70. Lyon, France: International Agency for Research on Cancer, 1997.
3. Klippel JH, ed. Primer on the rheumatic diseases. 12th ed. Atlanta, GA: Arthritis Foundation, 2001.
4. Björnådal L, Löfström B, Yin L, et al. Increased cancer incidence in a Swedish cohort of patients with systemic lupus erythematosus. Scand J Rheumatol 2002;31:66–71.
5. Ragnarsson O, Gröndal G, Steinsson K. Risk of malignancy in an unselected cohort of Icelandic patients with systemic lupus erythematosus. Lupus 2003;12:687–91.
6. Mellemkjær L, Andersen V, Linet MS, et al. Non-Hodgkin's lymphoma and other cancers among a cohort of patients with systemic lupus erythematosus. Arthritis Rheum 1997;40:761–8.
7. Gridley G, McLaughlin JK, Ekbom A, et al. Incidence of cancer among patients with rheumatoid arthritis. J Natl Cancer Inst 1993;85:307–11.
8. Isomäki HA, Hakulinen T, Joutsenlahti U. Excess risk of lymphomas, leukemia and myeloma in patients with rheumatoid arthritis. J Chronic Dis 1978;31:691–6.
9. Ekström K, Hjalgrim H, Brandt L, et al. Risk of malignant lymphomas in patients with rheumatoid arthritis and in their first-degree relatives. Arthritis Rheum 2003;48:963–70.
10. Thomas E, Brewster DH, Black RJ, et al. Risk of malignancy among patients with rheumatic conditions. Int J Cancer 2000; 88:497–502.
11. Kassan SS, Thomas TL, Moutsopoulos HM, et al. Increased risk of lymphoma in sicca syndrome. Ann Intern Med 1978; 89:888–92.
12. Zhang Y, Holford TR, Leaderer B, et al. Prior medical conditions and medication use and risk of non-Hodgkin lymphoma in Connecticut United States women. Cancer Causes Control 2004;15:419–28.
13. Holly EA, Bracci PM. Population-based study of non-Hodgkin lymphoma, histology, and medical history among human immunodeficiency virus-negative participants in San Francisco. Am J Epidemiol 2003;158:316–27.
14. Doody MM, Linet MS, Glass AG, et al. Leukemia, lymphoma, and multiple myeloma following selected medical conditions. Cancer Causes Control 1992;3:449–56.
15. Bernstein L, Ross RK. Prior medication use and health history as risk factors for non-Hodgkin's lymphoma: preliminary results from a case-control study in Los Angeles County. Cancer Res 1992;52:5510s–15s.
16. Engels EA, Chatterjee N, Cerhan JR, et al. Hepatitis C virus infection and non-Hodgkin lymphoma: results of the NCI-SEER multi-center case-control study. Int J Cancer 2004; 111:76–80.

17. Chatterjee N, Hartge P, Cerhan JR, et al. Risk of non-Hodgkin's lymphoma and family history of lymphatic, hematologic, and other cancers. Cancer Epidemiol Biomarkers Prev 2004;13:1415–21.
18. Ries LAG, Eisner MP, Kosary CL, et al, eds. SEER cancer statistics review, 1975–2001. Bethesda, MD: National Cancer Institute, 2004.
19. Perry C, von Holten V, Muir C, eds. International classification of diseases for oncology. 2nd ed. Geneva, Switzerland: World Health Organization, 1990.
20. Jaffe ES, Harris NL, Stein H, et al, eds. Pathology and genetics of tumours of haematopoietic and lymphoid tissues. World Health Organization classification of tumors: pathology and genetics. Lyon, France: IARC Press, 2001.
21. Kassan SS, Moutsopoulos HM. Clinical manifestations and early diagnosis of Sjögren syndrome. Arch Intern Med 2004; 164:1275–84.
22. Ioannidis JP, Vassiliou VA, Moutsopoulos HM. Long-term risk of mortality and lymphoproliferative disease and predictive classification of primary Sjögren's syndrome. Arthritis Rheum 2002;46:741–7.
23. Voulgarelis M, Dafni UG, Isenberg DA, et al. Malignant lymphoma in primary Sjögren's syndrome. A multicenter, retrospective, clinical study by the European Concerted Action on Sjögren's syndrome. Arthritis Rheum 1999;42:1765–72.
24. Royer B, Cazals-Hatem D, Sibilia J, et al. Lymphomas in patients with Sjögren's syndrome are marginal zone B-cell neoplasms, arise in diverse extranodal and nodal sites, and are not associated with viruses. Blood 1997;90:766–75.
25. Abbondanzo SL. Extranodal marginal-zone B-cell lymphoma of the salivary gland. Ann Diagn Pathol 2001;5:246–54.
26. Jaffe ES. Common threads of mucosa-associated lymphoid tissue lymphoma pathogenesis: from infection to translocation. J Natl Cancer Inst 2004;96:571–3.
27. Hoover R, Fraumeni JF Jr. Risk of cancer in renal-transplant recipients. Lancet 1973;2:55–7.
28. Birkeland SA, Storm HH, Lamm LU, et al. Cancer risk after renal transplantation in the Nordic countries, 1964–1986. Int J Cancer 1995;60:183–9.
29. Adami J, Gäbel H, Lindelöf B, et al. Cancer risk following organ transplantation: a nationwide cohort study in Sweden. Br J Cancer 2003;89:1221–7.
30. Serraino D, Piselli P, Angeletti C, et al. Risk of Kaposi's sarcoma and of other cancers in Italian renal transplant patients. Br J Cancer 2005;92:572–5.
31. Dharnidharka VR, Tejani AH, Ho PL, et al. Post-transplant lymphoproliferative disorder in the United States: young Caucasian males are at highest risk. Am J Transplant 2002;2:993–8.
32. Baecklund E, Askling J, Rosenquist R, et al. Rheumatoid arthritis and malignant lymphomas. Curr Opin Rheumatol 2004;16:254–61.
33. Cerhan JR, Anderson KE, Janney CA, et al. Association of aspirin and other non-steroidal anti-inflammatory drug use with incidence of non-Hodgkin lymphoma. Int J Cancer 2003;106:784–8.
34. Baecklund E, Ekbom A, Sparen P, et al. Disease activity and risk of lymphoma in patients with rheumatoid arthritis: nested case-control study. BMJ 1998;317:180–1.
35. Kinlen LJ. Malignancy in autoimmune diseases. J Autoimmun 1992;5(suppl A):363–71.
36. Kamel OW, van de Rijn M, Weiss LM, et al. Reversible lymphomas associated with Epstein-Barr virus occurring during methotrexate therapy for rheumatoid arthritis and dermatomyositis. N Engl J Med 1993;328:1317–21.
37. Feng WH, Cohen JI, Fischer S, et al. Reactivation of latent Epstein-Barr virus by methotrexate: a potential contributor to methotrexate associated lymphomas. J Natl Cancer Inst 2004; 96:1691–702.
38. Sørensen HT, Mellemkjær L, Nielsen GL, et al. Skin cancers and non-Hodgkin lymphoma among users of systemic glucocorticoids: a population-based cohort study. J Natl Cancer Inst 2004;96:709–11.
39. Cerhan JR, Wallace RB, Folsom AR, et al. Medical history risk factors for non-Hodgkin's lymphoma in older women. J Natl Cancer Inst 1997;89:314–18.
40. Beiderbeck AB, Holly EA, Sturkenboom MCJM, et al. No increased risk of non-Hodgkin's lymphoma with steroids, estrogens and psychotropics (Netherlands). Cancer Causes Control 2003;14:639–44.
41. Brown SL, Greene MH, Gershon SK, et al. Tumor necrosis factor antagonist therapy and lymphoma development. Twenty-six cases reported to the Food and Drug Administration. Arthritis Rheum 2002;46:3151–8.
42. Rothman KJ, Greenland S. Matching. In: Rothman KJ, Greenland S, eds. Modern epidemiology. 2nd ed. Philadelphia, PA: Lippincott-Raven, 1998:147–61.
43. Jacobson DL, Gange SJ, Rose NR, et al. Epidemiology and estimated population burden of selected autoimmune diseases in the United States. Clin Immunol Immunopathol 1997; 84:223–43.